

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**761315Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**



IND 111691

## MEETING MINUTES

Novo Nordisk Inc.  
Attention: Patricia Wilson  
Director, Regulatory Affairs  
PO Box 846  
Plainsboro, NJ 08536

Dear Ms. Wilson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for concizumab.

We also refer to the telecon between representatives of your firm and the FDA on September 23, 2021. The purpose of the meeting was to discuss the strategy for a rolling submission for the initial BLA for the treatment of hemophilia B with inhibitors (HBwI) and hemophilia A with inhibitors (HAWI), including the content and timing of the rolling BLA submission portions.

A copy of the official minutes of the meeting/telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, contact Caden Brennen, Regulatory Project Manager, at 301-796-6591 or at [Caden.Brennen@fda.hhs.gov](mailto:Caden.Brennen@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Saleh Ayache, MD  
Clinical Reviewer  
Division of Nonmalignant Hematology  
Office of Cardiology, Hematology,  
Endocrinology, and Nephrology  
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes



## MEMORANDUM OF MEETING MINUTES

**Meeting Type:** Type B  
**Meeting Category:** Pre-BLA

**Meeting Date and Time:** September 23, 2021, 8-9 AM (ET)  
**Meeting Location:** Teleconference

**Application Number:** IND 111691  
**Product Name:** concizumab

**Indication:** routine prophylaxis of bleeding in patients with HBwl and HBwl

**Sponsor Name:** Novo Nordisk Inc.  
**Regulatory Pathway:** 351(a) of the Public Health Service Act

**Meeting Chair:** Saleh Ayache, MD  
**Meeting Recorder:** Caden Brennen, MS

### **FDA ATTENDEES**

Office of Cardiology, Hematology, Endocrinology, and Nephrology (OCHEN)  
Lisa Yanoff, MD, Deputy Director (Acting)

OCHEN, Division of Nonmalignant Hematology (DNH)  
Ann Farrell, MD, Director  
Albert Deisseroth, MD, PhD, Deputy Division Director  
Saleh Ayache, MD, Clinical Reviewer  
Fadi Nossair, MD, Clinical Reviewer

Office of Biostatistics (OB), Division of Biometrics IX  
Yeh-Fong Chen, PhD, Statistical Team Lead  
Huan Wang, PhD, Statistical Reviewer

Office of Clinical Pharmacology (OCP)  
Harisudhan Thanukrishnan, PhD, Clinical Pharmacology Reviewer

Division of Pharmacology & Toxicology (DPT-OCHEN)  
Pedro Del Valle, MS, PhD, FATS, Supervisor (Acting)  
Jeffrey Quinn, PhD, Nonclinical Reviewer

Office of Biotechnology Products (OBP)  
Zhenzhen Liu, Ph.D., Team Lead  
Tracy Denison, PhD, Product Quality Reviewer

OPQ, Office of Pharmaceutical Manufacturing Assessment (OPMA)

Reyes Candau-Chacon, PhD, OPMA reviewer

CDRH, Division of Immunology and Hematology Device

Lea Carrington, PhD, Division Director

Rong Rong, MD, Medical Officer

Dinuka DeSilva, PhD, CDRH Reviewer

Office of Regulatory Operations

Caden Brennen, MS, Regulatory Project Manager

**SPONSOR ATTENDEES**

**Novo Nordisk (US)**

Patty Wilson, Director, Regulatory Affairs

Robert Clark, VP Regulatory Affairs

Tiffany Chamberlain, Associate Manager, Regulatory Affairs

Stephanie Seremetis, Chief Medical Officer Haemophilia

**Novo Nordisk (DK)**

Josephine Skovgaard Rasmussen, Safety Surveillance Specialist

Flemming Luther Søndergaard, Principal Statistician

Christian Ruzanski, Senior Scientist, Clinical Bioanalysis

Jakob Oemar Gjørret, Diagnostic Director

Katarina Cepo, International Medical Director, Haemophilia

Jesper Haaning, Project Vice President

Katrine Rasmussen, Global Regulatory Lead

Jane Møll Pedersen, Senior Director Regulatory Affairs, Rare Blood Disorders

Katrine Almind, Regulatory Affairs Specialist

Bérengère Paris, Senior Regulatory Affairs Professional

**1.0 BACKGROUND**

Concizumab is a humanized recombinant mAb of IgG4 isotype with a molecular weight of 149 kilodaltons. The product is designed to bind specifically to the Kunitz-domain-2 of TFPI and prevents TFPI from binding to and blocking the active site of the coagulation factor Xa (FXa).

Orphan designation was granted for concizumab for treatment of hemophilia A and hemophilia B on October 22, 2018, and July 22, 2019, respectively. Breakthrough Therapy Designation was granted for concizumab for hemophilia B patient with inhibitors (HBwl) on March 11, 2019.

The sponsor intends to apply for use of concizumab for routine prophylaxis of bleeding in patients with hemophilia B with inhibitors (HBwl) and hemophilia A with inhibitors (HAWl) for their initial BLA submission.

**U.S. Food and Drug Administration**

Silver Spring, MD 20993

[www.fda.gov](http://www.fda.gov)

The primary purpose and objective of this meeting is to obtain the Agency's input and agreement on:

- The strategy for a rolling submission for the initial BLA for the treatment of HBwl and HAWl, including the content and timing of the rolling BLA submission portions.

Additionally, the sponsor is also seeking for obtaining early input and agreement on the following:

- Relevant trials and data handling for the pooled safety evaluation
- Approach for providing financial certification and disclosure information
- Approach for using the concizumab-ELISA laboratory developed test (LDT) until the PMA for the concizumab-ELISA CDx kit is approved
- Data standardization plan
- Potential timing for pre-license inspections
- The stability program to support a commercial shelf-life of 24 months for the combination product

FDA sent Preliminary Comments to Sponsor on September 15, 2021.

## **2.0 DISCUSSION**

### **2.1. Questions and Responses**

Question 1: Does the Agency agree to the overall strategy for submission of a BLA for both HBwl and HAWl, which will include a request for Priority Review if supported by clinical data for HBwl?

**FDA Response: We agree on your overall strategy for BLA submission for both HBwl and HAWl. If you intend to request a priority review, your submission should include adequate justification.**

**Meeting Discussion: No discussion took place during the meeting.**

Question 2: Does the Agency agree to the proposed rolling submission strategy?

**FDA Response: Yes, we agree.**

**From a technical perspective (and not content related), the FDA agrees with the proposed documents/document locations found in Portion 1, Portion 2, and Appendix A.**

**Meeting Discussion:** No discussion took place during the meeting.

Question 3: Can Novo Nordisk expect any potential FDA Information Requests before the submission of the last portion of the BLA rolling submission?

**FDA Response:** Yes, you may receive FDA Information Requests before the submission of the last portion of the BLA if deemed appropriate or necessary by the Agency.

**Meeting Discussion:** No discussion took place during the meeting.

Question 4: Does the Agency agree to Novo Nordisk's proposed approach for data pooling in relation to the safety evaluation?

**FDA Response:** No. For the safety evaluation, we recommend that safety data from patients with hemophilia A and B with inhibitor be pooled separately from safety data from patients with hemophilia A without inhibitors. Therefore, phase 2 trial 4310, main + extension parts and phase 3a trial 4311 be pooled separately, from the safety data from trials 4159 and 4255.

We would like to remind you that the pooling strategy you proposed was not originally designed to perform any inferential statistical analyses or comparisons between treatment groups. For exploratory purpose and to avoid any misleading interpretation, please also summarize safety outcomes for each treatment group in the relevant study separately.

**Meeting Discussion:** The Sponsor stated that based on the FDA advice the presentation of the pooled safety data in the safety summary will include the combined inhibitor population as follows:

- HAwI+HBwI represents pooled data from 4310 + 4311
- HA represents pooled data from 4159 + 4255

The pooled dataset for 4159, 4255, 4310 and 4311 will be provided in section 5.3.5.3 with variables to filter on e.g., trial ID and hemophilia type. Also, safety outcomes will be summarized for each treatment group in the relevant studies separately.

The Agency agreed with the Sponsor's revised plan for presentation of the safety data, while advising the Sponsor should also provide confidence intervals for summarized results.

Question 5: Does the Agency agree with Novo Nordisk's planned approach for providing financial certification and disclosure information?

**FDA Response: No.** In addition to disclosure of financial interests for all investigators and subinvestigators in trials (4159, 4255, 4310, 4311), you should include financial disclosure for all investigators and subinvestigators in trial 3813 and trial 3986.

**Meeting Discussion:** No discussion took place during the meeting.

Question 6: Does the Agency agree to the planned approach for using the concizumab-ELISA (b) (4)

**FDA Response: The concizumab-ELISA is approved (b) (4) and with supplements. (b) (4)**

The concizumab-ELISA can only be utilized under conditions granted in IDE (b) (4) which is for use in dose adjustment in the treatment of patients with hemophilia A or B with or without inhibitors in concizumab clinical trials and compassionate use program (e.g., NN7415-4311, NN7415-4807) in participants ≥12 years of age at a single site (b) (4).

**Meeting Discussion:** The Sponsor asked, “Does the Agency agree to the planned approach for using the concizumab-ELISA LDT (b) (4)”

FDA indicated we would need to see the validation data in a supplement. Sponsor agreed to submit the validation data in a supplement to the IDE.

(b) (4)

FDA indicated we cannot agree to that at this time and to submit the requested information in a supplement. Sponsor agreed to submit the requested information.

Question 7: Does the Agency agree to Novo Nordisk's strategy for migrating legacy format datasets to CDISC standards?

**FDA Response:** From the technical perspective Novo Nordisk's strategy for migrating legacy format datasets to CDISC standards is acceptable. The legacy datasets that generate ADPP dataset should be included in the submission since ADaM dataset with pharmacokinetic parameters (ADPP) is migrated directly from the data in legacy format.

**Meeting Discussion:** No discussion took place during the meeting.

Question 8: Does the Agency agree to Novo Nordisk's planned approach for transfer of data from the phase 2 trials and the NIS to phase 3a trials?

**FDA Response:** Your approach for transfer of data from the phase 2 trials and the NIS to the phase 3a trials appears to be acceptable.

**Meeting Discussion:** No discussion took place during the meeting.

Question 9: Does the Agency agree with Novo Nordisk's planned approach to U.S. conventional units?

**FDA Response:** Your approach appears to be acceptable.

**Meeting Discussion:** No discussion took place during the meeting.

Question 10: Does the Agency agree these production slots are appropriate for a potential prelicense inspection at (b) (4)?

**FDA Response:** The drug substance target manufacturing dates are acceptable for the proposed submission dates. Please update the manufacturing schedule as the BLA submission approaches and/or if there are changes in the schedule. In addition, provide the manufacturing schedule for the drug product manufacturing facility

**Meeting Discussion:** No discussion took place during the meeting.

Question 11: Does the Agency agree that the outlined stability strategy and planned stability data for concizumab support a commercial shelf-life of 24 months for the final combination product?

**FDA Response: The Agency agrees that the stability strategy outlined supports the 24-month shelf-life.**

**Meeting Discussion: No discussion took place during the meeting.**

Question 12: Does the Agency agree to receive additional stability data as detailed in the meeting package no later than end of September 2022?

**FDA Response: The Agency agrees to receive additional stability data as detailed in the meeting package no later than the end of September 2022.**

**Meeting Discussion: No discussion took place during the meeting.**

#### **Additional CDRH Comments**

Device information should be located in the appropriate eCTD module, as recommended in the FDA's eCTD Technical Conformance Guide: Technical Specifications Document: "Guidance for Industry Providing Regulatory Submissions in Electronic Format —Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications" (<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM465411.pdf>).

When submitting a marketing application for the final finished combination product, provide the following information related to your device:

#### **1. Device Description Documentation**

- a. Provide a description of your device constituent design, including any novel features and/or functionalities. This should include drawings / diagrams of the device, descriptions of device components, or any other available information to explain the device design.
- b. Describe the principles of operation of your device.
- c. Describe any accessories or other devices labeled for use with your device.

#### **2. Design Control (21 CFR 820.30) – The application should include design documentation. The use of recognized standards and FDA guidance to inform design and testing is recommended, as applicable. For questions about design control documentation, we recommend that you reference the**

**FDA Design Control Guidance for Medical Device Manufacturers, <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddevgen/documents/document/ucm070642.pdf>. We recommend that the design control information provided in your application include the following:**

- a. Design Input Requirements (e.g., safety, performance, and reliability requirements of a device that are used as a basis for device design)
  - b. Design Output Specifications (e.g., device description, drawings, specifications, bill of materials, etc.)
  - c. Design Verification Plan/Summary Report, supporting data and traceability
  - d. Design Validation Plan/Summary Report, supporting data and traceability
  - e. Risk Management File
3. **Essential Performance – Identify essential performance requirements (EPR) for the device.**

**For each identified essential performance requirement, your marketing application should include verification and validation information of EPR specifications. While the final set of essential performance requirements should be based on your design control process, we are providing the following example EPRs for your device type. This is not an exhaustive list and product specific factors should influence your EPR selection.**

**Example pen injector EPRs:**

- **Delivered Volume Accuracy**
- **Injection Force**
- **Injection Time (if applicable)**

**Please refer to the FDA Guidance titled Guidance for Industry and FDA Staff: Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products issued in June 2013 (<https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm147095.pdf>) for more details.**

4. **Stability (ICH Q1) – Your stability program should include endpoints to verify that device essential performance is maintained at expiry. You may**

**exclude certain EPRs from the stability study if you can provide scientific rationale that the excluded EPR is unlikely to change over time.**

- 5. Shipping - Provide documentation for the final finished product to demonstrate that the device EPRs are met after shipping.**
- 6. Control Strategy – Provide a control strategy that ensures that the final finished combination product maintains its essential performance requirements. The control strategy may consist of, but is not limited to, lot release, in-process, control of incoming materials, purchasing controls, etc.**
- 7. Quality System - The marketing application should contain a complete summary of your base operating system as described in the FDA guidance titled Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products issued in January 2017 <https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM429304.pdf>.**

#### **Additional CMC Microbiology Comments**

**The FDA is providing additional product quality microbiology comments for you to consider during development of your commercial manufacturing process and preparation of your 351(a) BLA submission. These comments have been updated from the information included in the End of Phase 2 Meeting.**

**All facilities should be registered with the FDA at the time of the 351(a) BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Include in the BLA submission a complete list of the manufacturing and testing sites with their corresponding FEI numbers. A preliminary manufacturing schedule for the drug substance and drug product should be provided in the BLA submission to facilitate the planning of pre-license inspections during the review cycle. Manufacturing facilities should be in operation and manufacturing the product under review during the inspection.**

- Bioburden and endotoxin levels at critical manufacturing steps should be monitored using qualified bioburden and endotoxin tests. Bioburden sampling should occur prior to any 0.2 µm filtration step. The pre-established bioburden and endotoxin limits should be provided (3.2.S.2.4).**
- Bioburden and endotoxin data obtained during manufacture of three process qualification (PPQ) lots (3.2.S.2.5).**

- **Microbial data from three successful product intermediate hold time validation runs at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5).**
- **Chromatography resin and UF/DF membrane lifetime study protocols and acceptance criteria for bioburden and endotoxin samples. During the lifetime studies, bioburden and endotoxin samples should be taken at the end of storage prior to sanitization (3.2.S.2.5).**
- **Information and summary results from the shipping validation studies (3.2.S.2.5).**
- **Drug substance bioburden and endotoxin release specifications (3.2.S.4).**
- **Summary reports and results from bioburden and endotoxin test method qualification studies performed for in-process intermediates and the drug substance. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers (3.2.S.4).**

**The CMC Drug Product section of the 351(a) BLA (Section 3.2.P) should contain validation data summaries to support the aseptic processing operations. For guidance on the type of data and information that should be submitted, refer to the 1994 FDA Guidance for Industry “*Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*” at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072171.pdf>.**

**The following information should be provided in Sections 3.2.P.3.3 and/or 3.2.P.3.4, as appropriate.**

- **Identification of the manufacturing areas and type of fill line (e.g., open, RABS, isolator), including area classifications.**
- **Description of the sterilizing filter (size, membrane material, membrane surface area, etc.); sterilizing filtration parameters (pressure and/or flow rate), as validated by the microbial retention study (if a pump is used to**

filter-sterilize the drug product during routine operations, routine pressure monitoring upstream the sterilizing filter is expected); wetting agent used for post-use integrity testing of the sterilizing filter and post-use integrity test acceptance criteria.

- Parameters for filling, plunger placement, and capping of the cartridges.
- A list of all equipment and components that contact the sterile drug product (i.e., the sterile-fluid pathway) with the corresponding method(s) of sterilization and depyrogenation, including process parameters. The list should include single-use equipment.
- Processing and hold time limits, including the time limit for sterilizing filtration and aseptic filling.
- Sampling points and in-process limits for bioburden and endotoxin. Bioburden samples should be taken at the end of the hold time prior to the subsequent filtration step. Pre-sterile filtration bioburden limits should not exceed 10 CFU/100 mL.

The following study protocols and validation data summaries should be included in Section 3.2.P.3.5, as appropriate:

- Bacterial filter retention study for the sterilizing filter. Include a comparison of validation test parameters with routine sterile filtration parameters.
- Sterilization and depyrogenation of equipment and components that contact the sterile drug product. Provide summary data for the three validation studies and describe the equipment and component revalidation program.
- In-process microbial controls and hold times. Three successful product intermediate hold time validation runs should be performed at manufacturing scale, unless an alternative approach can be scientifically justified. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided.
- Isolator decontamination summary data and information, if applicable.

- Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs. Describe the environmental and personnel monitoring procedures followed during media fills and compare them to the procedures followed during routine production.
- Information and summary results from shipping validation studies. If the plunger in the cartridge is not secured by a rigid structure, the effects of varying air pressure on the plunger movement and potential breaches to the integrity of the sterile boundary during shipment should be addressed. Include data demonstrating that the plunger movement during air transportation does not impact product sterility.
- Validation of capping parameters, using a container closure integrity test.

The following product testing and method validation information should be provided in the appropriate sections of Module 3.2.P:

- Specification for the concentration of preservative by chemical analysis and the method used to quantify the preservative concentration. Preservative concentration should be tested at release and on stability at all test intervals.
- Antimicrobial effectiveness testing (APET) in accordance with USP <51>. The study should be performed with the lowest concentration of preservative indicated by the specification. APET should be conducted on the first three commercial lots of drug product placed on stability, at the beginning and end of the stability period.
- Container closure integrity testing. System integrity should be demonstrated initially and during stability. Container closure integrity method validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress ( $\leq 20$  microns). Container closure integrity testing should be performed *in lieu* of sterility testing for stability samples every 12 months (annually) until expiry.
- Information to demonstrate container closure integrity of the primary container after assembly in the pen injector.
- Summary report and results for qualification of the bioburden, sterility, and endotoxin test methods performed for in-process intermediates (if

applicable) and the finished drug product, as appropriate. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers. Provide full descriptions and validation of non-compendial rapid microbial methods.

- Summary report and results of the Rabbit Pyrogen Test conducted on three batches of drug product in accordance with 21 CFR610.13(b).
- Low endotoxin recovery studies. Certain product formulations have been reported to mask the detectability of endotoxin in the USP <85> *Bacterial Endotoxin Test* (BET). The effect of hold time on endotoxin detection should be assessed by spiking a known amount of standard endotoxin (RSE or purified CSE) into undiluted drug product and then testing for recoverable endotoxin over time.

#### **Additional CMC Feedback for Preparation of your BLA Submission**

1. To facilitate the Agency's review of the drug substance and drug product manufacturing process for concizumab, provide the information for all attributes, parameters, or controls proposed for routine commercial manufacturing as well as those evaluated during development and validation, in the tabular format provided below. Please provide a separate table for each unit operation. The tables should summarize information from Module 3 and may be submitted either to Module 1 or Module 3R. Note, this table does not replace other parts of Module 3 or impact the nature or amount of information included in those parts of Module 3.

| Process parameter/<br>operating parameter/<br>in-process control<br>(IPC) | Proposed Range for Commercial Manufacturing | Criticality classification <sup>1</sup> | Range assessed during process development studies | Range during process validation runs | Range from Clinical Study Lots | Justification of the proposed commercial acceptable range <sup>2</sup> |
|---------------------------------------------------------------------------|---------------------------------------------|-----------------------------------------|---------------------------------------------------|--------------------------------------|--------------------------------|------------------------------------------------------------------------|
|---------------------------------------------------------------------------|---------------------------------------------|-----------------------------------------|---------------------------------------------------|--------------------------------------|--------------------------------|------------------------------------------------------------------------|

<sup>1</sup>For example, critical process parameter, non-critical process parameter, as described in module 3.

<sup>2</sup>Provide a brief summary description (e.g., "development range", "validation range", or "platform experience"). To link to additional description for justification you may additionally include a link or reference to the appropriate section of the eCTD with more detail.

2. To facilitate the Agency's review of the control strategy for concizumab, provide information for critical quality attributes and process and product related impurities for the drug substance and drug product in the following tabular format. The tables should summarize information from module 3 and may be submitted either to module 1 or module 3R. These tables do

not replace other parts of Module 3 or impact the nature or amount of information included in those parts of Module 3. Attributes that are deemed to not be critical should also be justified in the BLA with the reasoning for that categorization.

| Critical Quality attributes<br>(including Process and Product related impurities for DS and DP) | Impact <sup>1</sup> | Source <sup>2</sup> | Analytical method <sup>3</sup> | Proposed control strategy <sup>4</sup> | Justification of the proposed control strategy <sup>5</sup> |
|-------------------------------------------------------------------------------------------------|---------------------|---------------------|--------------------------------|----------------------------------------|-------------------------------------------------------------|
|-------------------------------------------------------------------------------------------------|---------------------|---------------------|--------------------------------|----------------------------------------|-------------------------------------------------------------|

<sup>1</sup>What is the impact of the attribute, e.g., contributes to potency, immunogenicity, safety, efficacy.

<sup>2</sup>What is the source of the attribute or impurity, e.g., intrinsic to the molecule, fermentation, protein A column.

<sup>3</sup>List all the methods used to test an attribute in-process, at release, and on stability as applicable. For example, if two methods are used to test identity then list both methods for that attribute.

<sup>4</sup>List all the ways the attribute is controlled, e.g., in-process testing, validated removal by process, release testing, stability testing.

<sup>5</sup>Provide a brief description. In addition, you may provide links or references to appropriate sections of the eCTD that provide more detail.

3. To facilitate the Agency's assessment of the adequacy of the proposed commercial release specifications for concizumab drug substance (DS) and drug product (DP), provide information for each release specification in the tabular format provided below. Please provide a separate table for concizumab DS and DP, as described below. Each release specification should be described in a separate row. Add additional rows for additional release specifications, as needed. In general, include footnotes for each column of grouped results to indicate which lot numbers were used for each calculation of minimum-maximum range, and provide the number of batches (n=?) in the table also. The tables should summarize information from module 3 and may be submitted either to module 1 or module 3R. These tables do not replace other parts of Module 3 or impact the nature or amount of information included in those parts of Module 3.

| Release Specification for Concizumab Drug Substance |                   |                                                 |                                                            |                                                                                      |                                                    |                                                                                            |                                                                                           |
|-----------------------------------------------------|-------------------|-------------------------------------------------|------------------------------------------------------------|--------------------------------------------------------------------------------------|----------------------------------------------------|--------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|
| Attribute                                           | Analytical Method | Proposed Commercial Release acceptance criteria | Release results for development al batches (n=?) (min-max) | Release results for DS batches <sup>a</sup> (n=?) used in clinical studies (min-max) | Release results for DS PPQ batches (n=?) (min-max) | Release results for all DS lots <sup>b</sup> made using commercial process (n=?) (min-max) | Justification of specification (e.g. clinical experience, manufacturing capability, etc.) |

|                                                                                                                                                                                                                                                                                                                                                                                        |  |  |  |  |  |  |  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|--|--|--|--|--|--|
|                                                                                                                                                                                                                                                                                                                                                                                        |  |  |  |  |  |  |  |
|                                                                                                                                                                                                                                                                                                                                                                                        |  |  |  |  |  |  |  |
| <p>a. Include all batches used for any clinical testing, even from a different processes or scale. List each of the batch numbers included as footnote in the table.</p> <p>b. Include all lots with available release data that were manufactured following the proposed commercial process. Include a list of the batch numbers included in analysis as a footnote in the table.</p> |  |  |  |  |  |  |  |

| Release Specification for Concizumab Drug Product                                                                                                                                                                                                                                                                                                                                                         |                   |                                                 |                                                                               |                                                                      |                                                    |                                                                                                                |                                                                                           |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|-------------------------------------------------|-------------------------------------------------------------------------------|----------------------------------------------------------------------|----------------------------------------------------|----------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|
| Attribute                                                                                                                                                                                                                                                                                                                                                                                                 | Analytical Method | Proposed Commercial Release acceptance criteria | Release results for nonclinical and development al DP batches (n=?) (min-max) | Release results for clinical DP batches <sup>a</sup> (n=?) (min-max) | Release results for DP PPQ batches (n=?) (min-max) | Release results for all DP lots <sup>b</sup> made using commercial process, including PPQ lots (n=?) (min-max) | Justification of specification (e.g. clinical experience, manufacturing capability, etc.) |
|                                                                                                                                                                                                                                                                                                                                                                                                           |                   |                                                 |                                                                               |                                                                      |                                                    |                                                                                                                |                                                                                           |
|                                                                                                                                                                                                                                                                                                                                                                                                           |                   |                                                 |                                                                               |                                                                      |                                                    |                                                                                                                |                                                                                           |
| <p>a. Include all batches used in any clinical testing, regardless of scale, process, or manufacturing location, etc. List each of the batch numbers included as footnote in the table.</p> <p>b. Include all lots with available release data that were manufactured following the proposed commercial process. Include a list of the batch numbers included in analysis as a footnote in the table.</p> |                   |                                                 |                                                                               |                                                                      |                                                    |                                                                                                                |                                                                                           |

4. To facilitate the Agency's assessment of the adequacy of the stability specifications of concizumab DS and DP, provide stability information for storage at recommended condition for each stability specification in the example tabular format provided below. Please provide a separate table for concizumab DS and DP, as described below. Each stability specification should be described in a separate row. Add additional rows for additional stability specifications, as needed. If any stability specifications are different than the corresponding release specification for an analytical method that is used for both, then provide justification why different acceptance criteria are proposed for release and stability. Include footnotes to the tables to list the batch numbers that were used in each assessment, and justify any lots excluded from the assessment. Consider the data from all stability time points, not only release and end of proposed shelf-life. If a lot has not completed stability testing to the end of the

proposed shelf-life, include data from all time points that are currently available for that lot in the evaluation. The tables should summarize information from module 3 and may be submitted either to module 1 or module 3R. These tables do not replace other parts of Module 3 or impact the nature or amount of information included in those parts of Module 3.

| Stability Specification for Concizumab Drug Substance/Drug Product |                   |                               |                                                                                                                                                                                             |                                                                                   |
|--------------------------------------------------------------------|-------------------|-------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| Attribute                                                          | Analytical Method | Stability acceptance criteria | Stability results for batches stored at intended storage temperature (n=?)<br><br>Min – Max (Range for all available data from time 0 to proposed end of shelf life or currently available) | Justification of specification (e.g. stability data, clinical experience, , etc.) |
|                                                                    |                   |                               |                                                                                                                                                                                             |                                                                                   |
|                                                                    |                   |                               |                                                                                                                                                                                             |                                                                                   |

5. In your BLA submission, provide an evaluation of extractables and leachables, including a risk assessment, for both drug substance (DS) and drug product (DP). The BLA should include information that addresses the risk from potential leachables from the DS and DP Container Closure System (CCS) over the shelf-life of your product. The leachables studies may be performed as part of your stability protocol to support DS and DP expiry. Analysis of leachables should include organic non-volatile (e.g., HPLC-UV-MS), volatile (e.g., headspace GC-MS), semi-volatile (e.g., GC-MS), and metals (e.g., ICP-MS) species including their chemical identification and quantitation. Additional information regarding extractables and leachables should be provided per FDA Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics (1999).

A separate evaluation is also required for the potential generation of in-process leachables for DS and DP as a result of the product contact to equipment including disposables such as filters, containers, and bags. Data from a risk assessment should be provided to assure patient safety if in-process leachables are identified. However, testing might not be required (or necessary) if you provide scientific justification that the downstream purification/ process steps are expected to clear any potential in-process leachables.

6. Your shipping validation studies for DS and DP should include an assessment of product quality before and after shipment and be performed with product that is representative of the commercial manufacturing process, formulation, and container closure. Include in your original BLA submission results from shipping validation studies performed to support the physico-chemical stability of DS and DP. These studies should assess the impact of worst-case shipping conditions and potential temperature excursions on the critical quality attributes of the product and represent the spectrum of allowed packing arrangements of product within any secondary/tertiary packaging also. Include a summary table of all shipping lanes for concizumab from time of drug substance manufacturing shipping to all subsequent locations for DP manufacturing, labeling, packaging, etc. until the final product is ready for distribution. Include a description of any intermediate storage facilities where product may also be shipped for storage throughout this process, as applicable. Summarize for each shipping lane details of distance, method of transportation, and duration of the shipment, and indicate and justify which shipping validation data support that shipping lane.
7. To facilitate the Agency's assessment of the suitability of the analytical methods for release and stability testing of concizumab DS and DP and for in-process test methods, provide summarized results of method validation in the tabular format provided below. Please provide a separate table for each analytical method, as described below. Each parameter, e.g. specificity, precision, accuracy, etc. should be described in a separate row. Add additional rows for additional parameters, as needed. Study design should include a brief description of the testing material (batch information), the number of tests (e.g., the number of replicates, runs, plates, analysts, etc., if applicable), design of the experiment, approach of data reporting, and other important overview information regarding the validation of that parameter, as needed. Indicate in the table title the name of the method and all applicable programs where it is used such as DS release/stability, DP release/stability, or in-process testing.

|                                                                                                                                                                                                                        |              |                                                    |                    |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|----------------------------------------------------|--------------------|
| Summary of Validation Results for (insert Method) used for DS/DP release/stability, in-process testing, etc.                                                                                                           |              |                                                    |                    |
| Location of QC commercial testing site:                                                                                                                                                                                |              | Location where method was validated <sup>a</sup> : |                    |
| System Suitability Acceptance Criteria:                                                                                                                                                                                |              |                                                    |                    |
| Parameter                                                                                                                                                                                                              | Study Design | Acceptance Criteria                                | Validation Results |
|                                                                                                                                                                                                                        |              |                                                    |                    |
|                                                                                                                                                                                                                        |              |                                                    |                    |
| a: Provide a reference to supporting information and data in the BLA for method transfer, as applicable, for methods that were validated in a different site than where they will be tested for commercial QC testing. |              |                                                    |                    |

8. Provide the following information in a completed table similar to the one below for all drug master files (DMFs) referenced in your biologics license application:

| DMF # | DMF Type | DMF Holder | Item referenced | Link to Letter of Authorization | Comments (if needed) |
|-------|----------|------------|-----------------|---------------------------------|----------------------|
|       |          |            |                 |                                 |                      |
|       |          |            |                 |                                 |                      |

### Immunogenicity Feedback

9. Currently the data relevant to the assessment of immunogenicity are dispersed throughout different locations of the eCTD including 2.7.4 Summary of Clinical Safety, 5.3.1.4 Reports on Biopharmaceutical Studies and 5.3.5 Reports of Efficacy and Safety Studies. For the BLA file we recommend that the applicant provide the Integrated Summary of Immunogenicity in eCTD section 2.7.2.4 Special Studies or Section 5.3.5.3 Reports of Analysis of Data from More than One Study. This Integrated Summary of Immunogenicity should provide:
- Immunogenicity Risk Assessment- this section should provide a concise immunogenicity risk assessment specific to the therapeutic product, in accordance to the principles discussed in the FDA Guidance (2014) *Immunogenicity Assessment for Therapeutic Protein Product*. This section should include discussions on product quality -related factors and how these may impact the immunogenic potential of the product; patient-related factors including a discussion on how likely is the patient population and clinical indication to result in immunogenic responses to the product, and a section on trial design-related factors, with a discussion of how the clinical study conditions may facilitate an immunogenic response to the product.
  - Tiered strategy and Stage-Appropriate Bioanalytical Assays- This section should provide details on the tiered immunogenicity strategy that applicant followed in the clinical program, and validation summaries for the various immunogenicity assay methods that were developed throughout the program. In addition, this section should provide links to method development and validation reports for all the immunogenicity assays used in the various clinical studies supporting the application, particularly those used to test immunogenicity samples from the pivotal clinical study(ies).

- c) **Clinical Study Design and Sampling Strategy:** this section should provide the immunogenicity sampling plan(s) for all clinical studies that had immunogenicity assessment performed. This section should include as justification for pre-treatment, in-treatment, and post-treatment sampling time points for immunogenicity and pharmacokinetics, where applicable. This section should discuss how the immunogenicity program aims to reveal the incidence, persistence and clinical significance of anti-drug antibodies.
- d) **Clinical Immunogenicity Data Analysis-** This section should provide summary results of immunogenicity analysis for all clinical studies having immunogenicity component, including the results of linear and/or non-linear correlation analysis between anti-drug antibody status and titers with PK/PD/efficacy/safety (adverse-events) data. This section should include drug levels measured in the samples tested for anti-drug antibodies, and trace drug product lots used in the individual clinical studies. Discussion should examine the impact of any pre-existing antibodies on pharmacokinetics, safety and efficacy, the impact of treatment-emergent anti-drug antibodies on pharmacokinetics, pharmacodynamics, efficacy and safety.

**Meeting Discussion:** No discussion took place during the meeting.

### **3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION**

- The content of a complete application was discussed. The Agency agreed to the Sponsor's plan for a rolling submission.
- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

### **PREA REQUIREMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration

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are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.<sup>1</sup> In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email [Pedsdrugs@fda.hhs.gov](mailto:Pedsdrugs@fda.hhs.gov). For further guidance on pediatric product development, please refer to FDA.gov.<sup>2</sup>

### **PRESCRIBING INFORMATION**

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information<sup>3</sup> and Pregnancy and Lactation Labeling Final Rule<sup>4</sup> websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.

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<sup>1</sup> When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at

<https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

<sup>2</sup> <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>

<sup>3</sup> <https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information>

<sup>4</sup> <https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule>

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- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

## **DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS**

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing

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of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).
- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).
- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission “**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**” in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

### **SECURE EMAIL COMMUNICATIONS**

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to [SecureEmail@fda.hhs.gov](mailto:SecureEmail@fda.hhs.gov). Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

### **MANUFACTURING FACILITIES**

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the

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time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

| Site Name | Site Address | Federal Establishment Indicator (FEI) or Registration Number (CFN) | Drug Master File Number (if applicable) | Manufacturing Step(s) or Type of Testing [Establishment function] |
|-----------|--------------|--------------------------------------------------------------------|-----------------------------------------|-------------------------------------------------------------------|
| (1)       |              |                                                                    |                                         |                                                                   |
| (2)       |              |                                                                    |                                         |                                                                   |

Corresponding names and titles of onsite contact:

| Site Name | Site Address | Onsite Contact (Person, Title) | Phone and Fax number | Email address |
|-----------|--------------|--------------------------------|----------------------|---------------|
| (1)       |              |                                |                      |               |
| (2)       |              |                                |                      |               |

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h<sup>5</sup> and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*<sup>6</sup>. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

## **OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS**

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions*, and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*, be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA

<sup>5</sup> <https://www.fda.gov/media/84223/download>

<sup>6</sup> <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and>

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investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.<sup>7</sup>

### **NONPROPRIETARY NAME**

On January 13, 2017, FDA issued a final guidance for industry *Nonproprietary Naming of Biological Products*, stating that, for certain biological products, the Agency intends to designate a proper name that includes a four-letter distinguishing suffix that is devoid of meaning.

Please note that certain provisions of this guidance describe a collection of information and are under review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (PRA). These provisions of the guidance describe the submission of proposed suffixes to the FDA, and a sponsor's related analysis of proposed suffixes, which are considered a "collection of information" under the PRA. FDA is not currently implementing provisions of the guidance that describe this collection of information.

However, provisions of the final guidance that do not describe the collection of information should be considered final and represent FDA's current thinking on the nonproprietary naming of biological products. These include, generally, the description of the naming convention (including its format for originator, related, and biosimilar biological products) and the considerations that support the convention.

To the extent that your proposed 351(a) BLA is within the scope of this guidance, FDA will assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

### **4.0 ISSUES REQUIRING FURTHER DISCUSSION**

There were no issues requiring further discussion.

### **5.0 ACTION ITEMS**

No action items were identified during the meeting.

### **6.0 ATTACHMENTS AND HANDOUTS**

3 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

<sup>7</sup> <https://www.fda.gov/media/85061/download>

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
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/s/  
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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

IND 111691

**MEETING MINUTES**

Novo Nordisk, Inc.  
Attention: Lewis Pollack, PhD  
Senior Director, Regulatory Affairs  
800 Scudders Mill Road  
Plainsboro, NJ 08536

Dear Dr. Pollack:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for concizumab.

We also refer to the meeting between representatives of your firm and the Food & Drug Administration (FDA) on March 27, 2019. The purpose of the meeting was to discuss the clinical design of the Phase 3 trials (NN7415-4311 and NN7415-4307) for the prophylactic use in hemophilia A (HA) & hemophilia B (HB) patients with and without inhibitors to exogenous factors (VIII – HA, IX – HB).

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Thomas Iype, Regulatory Project Manager, at (240) 402-6861.

Sincerely,

*{See appended electronic signature page}*

Kathy Robie Suh, MD, PhD  
Clinical Team Leader  
Division of Hematology Products  
Office of Hematology & Oncology Products  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION**  
**CENTER FOR DRUG EVALUATION AND RESEARCH**

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B  
**Meeting Category:** End of Phase 2

**Meeting Date and Time:** March 27, 2019; 3:00 pm – 4:00 pm (ET)  
**Meeting Location:** 10903 New Hampshire Avenue  
White Oak Building 22, Conference Room: 1309  
Silver Spring, Maryland 20903

**Sponsor/Applicant Name:** Novo Nordisk, Inc.  
**Application Number:** IND 111691  
**Product Name:** Concizumab  
**Proposed Indications:** The proposed indications are as follows:

- Routine prophylaxis of bleeding in patients with hemophilia A (congenital factor VIII deficiency)
- Routine prophylaxis of bleeding in patients with hemophilia B (congenital factor IX deficiency)
- Routine prophylaxis of bleeding in patients with hemophilia A with inhibitors to FVIII
- Routine prophylaxis of bleeding in patients with hemophilia B with inhibitors to FIX

**Meeting Chair:** Kathy Robie Suh, MD, PhD  
**Meeting Recorder:** Thomas Iype, PharmD, RPh

**FDA ATTENDEES**

Division of Hematology Products

Ann T. Farrell, MD, *Division Director*

Virginia Kwitkowski, MS, ACNP-BC, *Associate Director for Labeling*

Kathy M. Robie Suh, MD, PhD, *Clinical Team Leader*

Saleh Ayache, MD, *Clinical Reviewer*

Division of Biostatistics V

Jingjing Ye, PhD, *Biostatistics Team Leader*

Division of Clinical Pharmacology V

Olanrewaju Okusanya, PharmD, MS, *Clinical Pharmacology Team Leader*

Christy John, PhD, *Clinical Pharmacology Reviewer*

Division of Hematology, Oncology & Toxicology  
Ramadevi Gudi, PhD, *Pharmacology/Toxicologist*

Clinical Outcomes Assessment Staff  
Selena Daniels, PharmD, MS, *Team Leader*

Division of Biotechnology Review and Research  
Susan Krishner, PhD, *Review Chief*  
Ram Sihag, PhD, *Reviewer*

## **SPONSOR ATTENDEES**

Jesper Haaning, *Project Vice President, Biopharm*  
Ummay Laila Hasan Syed, *Director, Regulatory Affairs, Biopharm 1*  
Ute Ina Dr. Friedrich, *Principal Clinical Pharmacologist*  
Trine Høyer Rose, *Senior Modelling Scientist, Quantitative Clinical Pharmacology*  
Eva Lisby Arp-Hansen, *Senior Global Regulatory Lead, RA Biopharm*  
Søren Can Tamer, *Principal Statistician, Biostatistics Biopharm 1*  
Katarina Cepo, *International Medical Manager, Biopharm Medical & Science*  
Josephine Skovgaard Rasmussen, *Senior Safety Surveillance Adviser, Safety Surveillance Biopharm*  
Ida Hilden, *Research Project Vice President*  
Stephanie Seremetis, *Corporate Vice President & Chief Medical Officer*  
Lewis Pollack, *Senior Director, Regulatory Affairs*  
Payal Mehta, *Specialist, Regulatory Affairs*  
Michelle Thompson, *Senior Director, Regulatory Affairs*

## **1.0 BACKGROUND**

Concizumab is a humanized recombinant monoclonal antibody directed against tissue factor pathway inhibitor resulting in coagulation. The applicant is seeking advice on the clinical design of their Phase 3 trials (NN7415-4311 and NN7415-4307) for the prophylactic use in hemophilia A (HA) & hemophilia B (HB) patients with and without inhibitors to exogenous factors (VIII – HA, IX – HB). The applicant is conducting a Phase 2 study (NN7415-4255) in patients with severe hemophilia A without inhibitor to factor VIII and another Phase 2 study (NN7415-4310) in patients with hemophilia A and B with inhibitors to factors.

## **2.0 DISCUSSION**

**Question 1:** *Does the FDA agree that the completed nonclinical program is sufficient for the phase 3 trials and for the filing of a Biological License Application (BLA)?*

### **FDA Response to Question 1:**

Yes, no additional nonclinical studies are required for the phase 3 trials. All studies appear to be sufficient for filing the BLA. Any final decisions on the adequacy of the studies at filing will be a review issue.

**Discussion:** No discussion occurred.

**Question 2:** Does the Agency agree that the phase 2 data support the initiation of the proposed phase 3 pivotal trials in adult and adolescent hemophilia A (HA) and hemophilia B (HB) patients (trial 4307) and hemophilia A with inhibitors (HAwI) and hemophilia B (HBwI) patients (trial 4311)?

**FDA Response to Question 2:** Yes, we agree.

**Discussion:** No discussion occurred.

**Question 3:** Does the Agency agree to the proposed design of the phase 3 trial to support the indication of routine PPX in adult and adolescent HAwI and HBwI patients, including:

- a) Primary endpoint and primary analyses (Section 10.3.4.1 – Introduction and Part A)
- b) Confirmatory secondary endpoints and secondary analyses (Section 10.3.4.1-B)
- c) Chosen estimands, handling of missing data and sample size (Section 10.3.4.1-C).
- d) Handling of patients who discontinue treatment (Section 10.3.4.1-D)
- e) Patient population – number of patients and duration of exposure and the data to support the initial BLA for the indication in HBwI and subsequent filing for HAwI.(Section 10.3.4.1-E)
- f) Duration of treatment (Section 10.3.4.1-F)
- g) Safety monitoring (Section 10.3.4.1-G)

**FDA Response to Question 3:**

- a) Primary endpoint and primary analyses (Section 10.3.4.1 – Introduction and Part A)

The proposed primary endpoint appears to be acceptable.

Regarding the primary analyses, it is unclear if patient follow-up time is the same as exposure time. For NB regression model, we recommend you consider modeling the patient's number of bleeds as a function of randomization and including the time that each patient stays in the study (the length of the efficacy period) as an offset in the model.

In addition, you have included interactions between hemophilia type and bleeding frequencies. Given the sample size, please consider if you have enough power to evaluate differential benefits in the interactions.

If you expect excessive zero bleedings during treatment period, please consider analysis plan to account for this.

- b) Confirmatory secondary endpoints and secondary analyses (Section 10.3.4.1-B)

You have not provided detailed analysis plan on the PRO endpoints including but not limited to PRO frequencies, timing of the analysis, and missing data considerations.

*c) Chosen estimands, handling of missing data and sample size (Section 10.3.4.1-C).*

1. It appears that your primary analysis is based on FAS rather than ITT (intent-to-treat) population. Your primary analysis should be conducted on ITT population.
2. Please clarify what alternative estimators and corresponding estimates and sensitivity analyses will be established.
3. Please clarify the combined power.
4. You have not provided detailed analysis plan on how you plan to handle missing data.
5. We were unable to verify your sample size calculation. Please provide your software or source code.

*d) Handling of patients who discontinue treatment (Section 10.3.4.1-D)*

Please provide details on how you would account for the patients who discontinued treatment in your analyses.

*e) Patient population – number of patients and duration of exposure and the data to support the initial BLA for the indication in HBwI and subsequent filing for HAwI.(Section 10.3.4.1-E)*

It is premature to comment on the adequacy of the data to support initial BLA. The patient population, of patients with HAwI and HBwI, appears to be acceptable. The number of patients with HBwI for the proposed phase 3 trial (18 patients) appears to be small. Please provide justification in your protocol. Also, see response to question 3c.

*f) Duration of treatment (Section 10.3.4.1-F)*

The duration of concizumab exposure of at least 24 weeks appears to be reasonable, however, data from longer exposure may be required to support your proposed indication.

*g) Safety monitoring (Section 10.3.4.1-G)*

The safety endpoints and the rules for putting enrollment on hold appear to be reasonable.

Your study synopsis did not specify which type of on demand treatment will be used in the control. Also, you should provide justification for comparing your drug to on demand treatment (no prophylaxis) given there are approved drugs for the indication.

Also, we suggest that Arm 4, which includes rolled over patients from Arm 1 and Arm 2 upon completion of the main phase of the study, should be separated from trial NN7415-4311, i.e., as an extension study.

**Discussion:** For both Questions 3 and 4: The Sponsor confirmed that all randomized patient data will be included in the primary analysis. However, any bleeds post discontinuation for those patients that permanently discontinue from the study will not be included in the primary analysis. The Sponsor stated they will make every effort to minimize missing data. The Agency commented that some provision should be made to collect data on bleeds that occur post-discontinuation to document rebound bleeding that may occur. The Agency recommended to consider sensitivity analysis on accounting the rebound bleeds post-discontinuation. The FDA does not object to or agree with the proposed number of patients in the Phase 3 study. The adequacy of the data to support an application will remain a review issue.

The Sponsor clarified that the extension arm (arm 4) is being included as part of the Phase 3 study because of logistic/administrative reasons to facilitate follow-up and retention of patients.

The Agency commented that Wilcoxon signed rank test ignores different follow-up time for each patient and may be statistically underpowered statistics compared to parametric approaches like Negative Binomial regression model. The Sponsor will submit supportive document to justify the approach.

The Agency commented that non-inferiority analysis comparing prophylaxis vs on demand treatment is not appropriate. The Sponsor stated that all comparisons of on demand vs. prophylaxis will be superiority analyses. The Agency requested further justification on non-inferiority margin and recommended the Sponsor to follow FDA CDER guidance on Non-inferiority, including but not limited to patient-level data, inclusion of within and between-study variability, consideration of heterogeneity of the population, frequency of assessment, missed assessments, and efficacy definition. The adequacy and magnitude of the NI margin will remain a review issue.

**Question 4:** Does the Agency agree to the proposed design of the phase 3 trial to support the indication of routine PPX in adult and adolescent HA and HB patients, including:

- a) Primary endpoint and primary analyses (Section 10.3.4.2 - Introduction and Part A)
- b) Confirmatory secondary endpoints and secondary analyses (Section 10.3.4.2 – B)
- c) Chosen estimands, handling of missing data and sample size (Section 10.3.4.2 – C)
- d) Handling of patients who discontinue treatment (Section 10.3.4.2 -D)
- e) Patient population (Section 10.3.4.2 – E)
- f) Duration of treatment (as per trial 4311)
- g) Safety monitoring (as per trial 4311)

**FDA Response to Question 4:**

- a) Primary endpoint and primary analyses (Section 10.3.4.2 - Introduction and Part A)

The proposed primary endpoint appears to be acceptable. Please refer to responses to Question 3A.

*b) Confirmatory secondary endpoints and secondary analyses (Section 10.3.4.2 – B)*

The secondary endpoint of ABR for concizumab treated patients compared to the patient's previous prophylaxis in HA and HB may be acceptable. However, you should provide more detailed information on the method of the analysis. We also recommend including secondary endpoint(s) of patient-reported hemophilia-related symptoms, e.g., based on Haem-A-QoL questionnaire, in your phase 3 trial. Provide copies of the instruments that you propose to use in your trial. We recommend using no more than a 7-day recall period for patient reported outcomes instruments due to the risk of recall bias.

*c) Chosen estimands, handling of missing data and sample size (Section 10.3.4.2 – C)*

We disagree with your approach to determine the non-inferiority margin for the first confirmatory second endpoint. Your approach did not take into consideration of the within-study variability and your approach did not calculate the margin according to FDA guidance. We recommend you implement the approaches of combining multiple studies and the 95%-95% fixed margin approach for calculating the margin provided/recommended in the FDA Guidance for Industry: Non-Inferiority Clinical Trials to Establish Effectiveness. Here is the link to the guidance: <https://www.fda.gov/downloads/Drugs/Guidances/UCM202140.pdf>

Also, see response to question 3c.

*d) Handling of patients who discontinue treatment (Section 10.3.4.2 -D)*

Please refer to response to Question 3D.

*e) Patient population (Section 10.3.4.2 – E)*

The patient population, of patients with HA and HB, appears to be acceptable. However, we recommend that you redesign your study to have two separate parallel designed studies--- one for patients with hemophilia A and one for patients with hemophilia B. If in the future, you decide to conduct two separate trials for HA and HB patients, respectively, sample size and power analyses should be revised correspondingly. Also, see response to question 4a-d.

*f) Duration of treatment (as per trial 4311)*

The duration of concizumab exposure of at least 24 weeks appears to be reasonable.

*g) Safety monitoring (as per trial 4311)*

The safety endpoints and rules for putting enrollment on hold appears to be reasonable.

**Discussion:** See Discussion under Question 3.

Regarding the patient population, the Sponsor stated HA and HB were being studied in the same study because of logistical/administrative reasons. FDA agreed that it is acceptable to include both HA and HB in the same phase 3 study; however, the study must have adequate power and enrollment to support distinct analysis for each HA and HB. The Sponsor agreed.

For the “first confirmatory secondary objective” the Sponsor clarified that the effect of the patient’s previous prophylaxis treatment will be derived from data collected in the observational non-interventional study 4322. FDA commented that the application should include the report/data from 4322. Acceptability of results will be a review issue.

The Agency stated that the Haem-A-QoL Physical Health domain had been previously included in labeling and would be a reasonable option to use in their planned trials. The Agency stated that use of the SF-36v2 could be acceptable, but that the Sponsor should submit evidence to support its content relevance for their target population for review. The Agency has some concerns that items that ask about ‘body pain’ in the SF-36v2 Bodily Pain domain may not fully assess hemophilia-related pain (i.e., joint pain). The Agency offered to have a COA-focused meeting with the Sponsor (after review of the qualitative data) to further discuss their COA measurement strategy to best capture the patient experience in their trials.

**Post-Meeting Comment:** To mitigate some concerns surrounding the Bodily Pain domain, the Agency suggests that the Sponsor consider administering a single NRS item that assesses joint pain.

**Question 5:** *Does the Agency agree that the phase 2 data generated in HA, HAwI and HBwI patients support the extrapolation to and inclusion of HB patients in phase 3?*

**FDA Response to Question 5:** Your approach of including patients with HB in the phase 3 clinical program appears to be reasonable.

**Discussion:** No discussion occurred.

**Question 6:** *Does the Agency agree with the dose selected for the two planned phase 3 trials in adult and adolescents?*

**FDA Response to Question 6:** No, you have not provided sufficient information to support your dose. It is not clear if you have adequately evaluated your data to determine what exposure you are targeting, the impact that exposure is expected to have on your PD endpoints, how that is expected to translate to ABR reduction, and the probability of patients achieving the expected exposure, over exposure, and under exposure, based on your

proposed doses, while taking into consideration, the patients intrinsic (e.g weight and age) and extrinsic factors, given that you intend to enroll adolescents in this study and you indicate that covariates such as measures of body size did not have an impact on drug clearance.

We recommend as part of your dose justification you also evaluate the relationship between exposure, your PD endpoints, and probability of ABR reduction to confirm your target PD concentration used for dose selection and use modeling and simulation to support and justify your proposed dose for your intended population.

**Discussion:** The Sponsor provided data indicating that concentrations greater than 200 ng/mL were associated with a decrease in ABR and stated that their current data does not indicate that higher concentrations are associated with thrombotic events. The Agency asked if there were any plans for intra-patient dose escalations due to a lack of response. The Sponsor stated that there are no plans for that at this time. The Agency noted the Sponsor has only explored multiple doses up to 0.25 mg/kg/day with dose escalations. The Agency stated that the adequacy of their selected doses will be a review issue.

**Question 7:** *For phase 3, does the Agency agree with our plans for treatment of breakthrough bleeds?*

**FDA Response to Question 7:** We recommend that one concomitant breakthrough bleeding product should be prespecified to each subpopulation i.e., FVIII for patients with HA, FIX for HB and NovoSeven or FEIBA for patients with HAwI or HBwI. Clinical data on concomitant breakthrough bleeding and dosage should be collected.

**Discussion:** No discussion occurred.

**Question 8a:** *Are the planned PK data adequate for BLA and sBLA filings and labeling?*

**FDA Response to Question 8a:** Given that you are evaluating a new regimen and the number of patients in your studies, we recommend that you collect PK from all patients. Sparse sampling (excluding troughs alone) may be adequate for some adult patients.

**Discussion:** No discussion occurred.

**Question 8b:** *Will the above strategy support a label that allows patients to rotate their injection between the three described anatomical locations?*

**FDA Response to Question 8b:** We recommend that a future BLA filing include proposed Instructions for Use for the intended population who will be administering the product.

**Discussion:** No discussion occurred.

**Question 8c:** *Does the Agency agree that the intrinsic/extrinsic factor analysis is adequately addressed for the BLA?*

**FDA Response to Question 8c:** We recommend that you conduct a complete exposure response analysis that incorporates covariates such as body weight, BMI, body surface area, baseline platelet count, baseline free TFPI, race/ethnicity, age group, baseline albumin, baseline ALT (above/below limit), and creatinine clearance (GFR) etc to understand the impact of these intrinsic/extrinsic factors on the probability of ABR reduction and address the need, if any, for dose adjustments.

**Discussion:** No discussion occurred.

**Question 9a:** *Does the agency agree that a Ligand Binding assay should be developed and validated, and if it shows better sensitivity used for the phase 3 program?*

**FDA Response to Question 9a:** FDA agrees with your plan to develop a ligand binding assay for the phase 3 program. In addition, it may be useful to know whether samples that test positive for NAb in the ligand binding assay also test positive in the coagulation assay.

FDA recommends that you provide a summary of the validation exercise, including supporting data, a summary of the development data supporting assay suitability for parameters not assessed in the validation exercise, and the assay SOPs to the FDA for review prior to testing clinical samples from pivotal trials. Store patient samples under appropriate storage conditions until an assay(s) has been developed. Please see the following references for advice and guidance:

References:

1. Guidance for Industry: Immunogenicity Testing of Therapeutic Protein Products – Developing and Validating Assays for Anti-Drug Antibody Detection. 2019.  
<https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm629728.pdf>
2. Guidance for Industry: Immunogenicity Assessment for Therapeutic Protein Products. 2014.  
<https://www.fda.gov/downloads/drugs/guidances/ucm338856.pdf>

**Discussion:** No discussion occurred.

**Question 9b:** *Does the Agency agree to the planned immunogenicity sampling and analysis plan?*

**FDA Response to Question 9b:** Your immunogenicity sampling and analysis plan are reasonable. The assessment of the adequacy of your proposed plan will be a BLA review issue.

**Discussion:** No discussion occurred.

### 3.0 OTHER IMPORTANT INFORMATION

#### **PREA REQUIREMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email [Pedsdrugs@fda.hhs.gov](mailto:Pedsdrugs@fda.hhs.gov). For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>

#### **DATA STANDARDS FOR STUDIES**

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See <http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>), as well as email access to the eData Team ([cdcr-edata@fda.hhs.gov](mailto:cdcr-edata@fda.hhs.gov)) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a [Study Data Standards Resources](#) web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that started on or before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The [FDA Study Data Technical Conformance Guide](#) (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the [FDA Study Data Standards Resources](#) web site. When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>.

## **LABORATORY TEST UNITS FOR CLINICAL TRIALS**

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, [Study Data Standards Resources](#) and the CDER/CBER Position on Use of SI Units for Lab Tests website found at <https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf>.

## **SUBMISSION FORMAT REQUIREMENTS**

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: <http://www.fda.gov/ectd>.

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway>.

## **OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS**

The Office of Scientific Investigations (OSI) requests that the items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in

submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications:

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf>

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>.

### **PATIENT-FOCUSED ENDPOINTS**

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf>

### **NEW PROTOCOLS AND CHANGES TO PROTOCOLS**

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
  - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
  - Other significant changes
  - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

#### **UNITED STATES PATIENT POPULATION**

FDA expects sponsors to enroll participants who are relevant to the planned use of the drug in the US population. Describe the steps you are taking to ensure that the clinical trial population will be relevant to the US patient population that will receive the drug. Include a discussion of participation of US vs. non-US sites and discuss whether the subjects likely to be enrolled will adequately represent the US patient population in terms of disease characteristics, sex, race/ethnicity, age, and standards of care. See 21 CFR 312.33(a)(2) and 21 CFR 314.50(d)(5)(v) and the Guidance for Industry, Collection of Race and Ethnicity Data in Clinical Trials (available at: <https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126396.pdf>) and for more information.

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

#### **4.0 ISSUES REQUIRING FURTHER DISCUSSION**

We make reference to section 2.0 (DISCUSSION).

#### **5.0 ACTION ITEMS**

We make reference to section 2.0 (DISCUSSION).

#### **6.0 ATTACHMENTS AND HANDOUTS**

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
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/s/  
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KATHY M ROBIE SUH  
04/04/2019 10:13:29 AM

## CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

|                                                                          |                                                                                                                                                                             |
|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| IND/NDA/BLA #                                                            | 111691                                                                                                                                                                      |
| Request Receipt Date                                                     | 01/10/2019                                                                                                                                                                  |
| Product                                                                  | Concizumab (mAb)                                                                                                                                                            |
| Indication                                                               | Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in hemophilia B patients with inhibitors                                                        |
| Drug Class/Mechanism of Action                                           | Concizumab is a humanized recombinant monoclonal antibody (mAb) of IgG4 targeting tissue factor pathway inhibitor (TFPI); one of the inhibitors in the coagulation cascade. |
| Sponsor                                                                  | Novo Nordisk                                                                                                                                                                |
| ODE/Division                                                             | OHOP/DHP                                                                                                                                                                    |
| Breakthrough Therapy Request(BTDR) Goal Date (within 60 days of receipt) | 03/09/2019                                                                                                                                                                  |

*Note: This document must be uploaded into CDER's electronic document archival system as a **clinical review: REV-CLINICAL-24 (Breakthrough Therapy Designation Determination)** even if the review is attached to the MPC meeting minutes and will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Link this review to the incoming BTDR. Note: Signatory Authority is the Division Director.*

### **Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.**

**1. Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):**

The proposed indication is that Concizumab is indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult patients with hemophilia B with inhibitor (HBwI).

**2. Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?**

☐ YES ☒ NO

**3. Was the BTDR submitted to a PIND?**

☐ YES ☒ NO

If "Yes" do not review the BTDR. The sponsor must withdraw the BTDR. BTDR's cannot be submitted to a PIND.

*If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:*

**4. Consideration of Breakthrough Therapy Criteria:**

a. Is the condition serious/life-threatening<sup>1</sup>?

☒ YES ☐ NO

*If 4a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:*

<sup>1</sup> For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

- b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?
- ☒ YES the BTDR is adequate and sufficiently complete to permit a substantive review
- ☐ Undetermined
- ☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore the request must be denied because (check one or more below):
- i. Only animal/nonclinical data submitted as evidence ☐
  - ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
  - iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
  - iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
  - v. No or minimal clinically meaningful improvement as compared to available therapy<sup>2</sup>/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

**5. Provide below a brief description of the deficiencies for each box checked above in Section 4b:**

*If 4b is checked “No”, BTDR can be denied without MPC review. Skip to number 6 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC’s input is desired. If this is the case, proceed with BTDR review and complete Section II). If the division feels MPC review is not required, send the completed BTDDRT to Miranda Ragqio for review. Once reviewed, Miranda will notify the MPC Coordinator to remove the BTDR from the MPC calendar. If the BTDR is denied at the Division level without MPC review, the BTDR Denial letter still must be cleared by Miranda Ragqio, after division director and office director clearance.*

*If 4b is checked “Yes” or “Undetermined”, proceed with BTDR review and complete Section II, as MPC review is required.*

**6. Clearance and Sign-Off (no MPC review)**

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}

Team Leader Signature: {See appended electronic signature page}

Division Director Signature: {See appended electronic signature page}

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**Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.**

**7. A brief description of the drug, the drug’s mechanism of action (if known), the drug’s relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.**

- Information regarding the disease and intended population for the proposed indication.
- Disease mechanism (if known) and natural history (if the disease is uncommon).

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<sup>2</sup> For a definition of available therapy refer to Guidance for Industry: “Expedited Programs for Serious Conditions—Drugs and Biologics” <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

Concizumab is a humanized recombinant monoclonal antibody (mAb) of immunoglobulin G4 (IgG4) targeting tissue factor pathway inhibitor (TFPI), one of the inhibitors in the coagulation cascade. Concizumab is indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult patients with hemophilia B with inhibitor (HBwI).

Hemophilia B is an X-linked congenital bleeding disorder caused by deficiency of factor IX (FIX). Bleeding tendency is correlated with severity of factor deficiency. Hemophilia B with inhibitors is a serious and life-threatening disease associated with significant morbidities including multiple episodes of joint, muscle and deep tissue bleeding which can be life- and/or limb-threatening <sup>(1)</sup>. It is estimated that the incidence of FIX inhibitors is between of 1.5–3% of all treated patients with hemophilia B. Approximately 80% of the inhibitors that develop to FIX are of the high responding type, i.e., have a robust anamnestic response (high titer of the inhibitor). According to the World Federation of Haemophilia Annual Global Survey 2016, there are an estimated 64 HBwI patients in the USA with prevalence of 1 in 7 million (ultra-rare disease) <sup>(2,3)</sup>.

There is one approved prophylaxis product for hemophilia B with inhibitor (HBwi), FEIBA (FEIBA, Baxter Healthcare Corporation). FEIBA is a plasma-derived activated prothrombin complex concentrate which contains in addition to Factor IX prothrombin, Factor VII and Factor X.

## 8. Information related to endpoints used in the available clinical data:

- a. *Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.*

The hallmark of hemophilia B is repeat bleeding into the joint and deep soft tissue. The analysis of the frequency of the bleeding is required to assess the clinical efficacy of treatment. The sponsor stated that the primary endpoint that will be used throughout the clinical development of concizumab is the number of treated bleeds over time. The key secondary endpoints were the number of spontaneous bleeding episodes and number treatment emergent adverse event (TEAEs). The same primary and the secondary endpoints will be used for the registration trials, which will be discussed with the Sponsor on March 2019.

- b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:
- *A clinical endpoint that directly measures the clinical benefit of a drug (supporting traditional approval).*
  - *A surrogate/established endpoint that is known to predict clinical benefit of a drug (i.e., a validated surrogate endpoint that can be used to support traditional approval).*
  - *An endpoint that is reasonably likely to predict clinical benefit of a drug (supporting accelerated approval), and the endpoint used in a confirmatory trial or trials to verify the predicted clinical benefit.*

The approval of FEIBA for the same indication, of routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients with hemophilia A and B with inhibitors, being sought here was based on a Phase 3 randomized, multicenter, open-label, clinical study in 36 patients with hemophilia A (33 patients) or B (3 patients) with high titer inhibitors or low-titer inhibitors refractory to factor VIII (FVIII) or factor IX (FIX) treatment. Nineteen subjects (2 patients with HBwI) randomized to the on-demand arm received FEIBA for the treatment of acute bleeding episodes per the dose and dosing regimen recommended. The primary outcome was a reduction in the annualized bleeding rate (ABR) for all types of bleed among patients on prophylaxis as compared to those treated on-demand. ABR is also the standard reporting measure in other clinical trials in the literature. ABR can be used to compare between treatment arms as well as inpatient comparisons before and after treatment interventions.

The efficacy analysis of the primary efficacy endpoint of the annualized bleeding rate (ABR) during prophylaxis showed a 73% reduction in the median ABR in patients received prophylactic FEIBA 7.9 compared to patients received on demand treatment 28.7. ABR analysis by site (e.g. joint, non-joint) and cause of bleed (e.g. spontaneous, traumatic), prophylactic treatment with FEIBA resulted in a greater than 50% reduction. In addition, 3 (18%) patients on prophylaxis experienced no bleeding episodes, whereas none treated on demand were bleeding episode-free.

- c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

N/A

**9. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:**

- If the available therapies were approved under accelerated approval, provide the information for the endpoint used to support accelerated approval and the endpoint used to verify the predicted clinical benefit.*
- In addition to drugs that have been approved by FDA for the indication, also identify those treatments that may be used off-label for that indication.*

The current standard of care available for patients with hemophilia B is FIX replacement with recombinant or plasma-derived factor products. The presence of inhibitors in patients with hemophilia B generally precludes the use of FIX replacement therapy or FEIBA due to, lack of efficacy as the antibodies would clear the exogenous FIX and, it is likely that the exposure would increase the inhibitor titer due to an anamnestic response (patients with HBwI usually high-responding). Also, FEIBA which is approved for HA wI and HB wI has data for only 1 patient with HBwI who received the product.

**10. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation<sup>3</sup>.**

None for the same indication. Emacizumab was granted breakthrough therapy designation on September 2015 for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and adolescents  $\geq 12$  years old with hemophilia A with FVIII inhibitors.

The sponsor of Emacizumab to support the BTDR designation submitted the preliminary results of a Phase I/II open label study of 16 patients with hemophilia A with inhibitor. The primary endpoint was reduction in ABR of each patient which was a comparison between the 6 months prior to starting the study drug and the duration on the study drug <sup>(4)</sup>.

**11. Information related to the preliminary clinical evidence:**

- a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design<sup>4</sup>, trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

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<sup>3</sup> Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

<sup>4</sup> Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

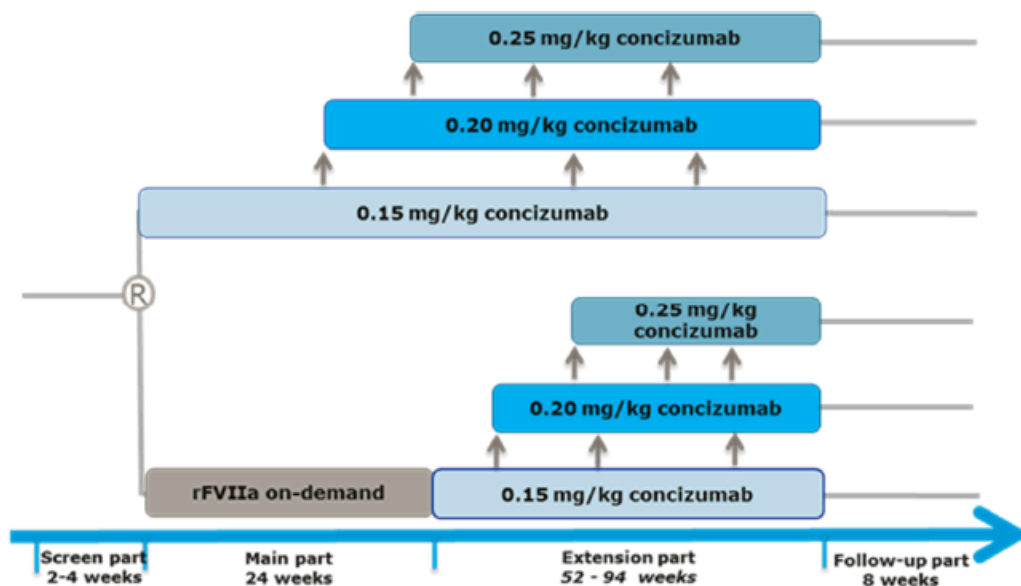
- Trial NN7415-4310 was a multinational, multi-center, randomized, open-label, controlled trial evaluating the efficacy and safety of prophylactic administration of concizumab administered S.C. once daily in patients with hemophilia A and B with inhibitors. Patients in concizumab arm were to receive a loading dose of 0.5 mg/kg concizumab as first dose followed by one week of concizumab dosing of 0.15 mg/kg.
  - A total of 26 patients with hemophilia A or B with inhibitors were randomized in 2:1 ratio to receive concizumab prophylaxis or rFVIIa on-demand treatment. There were 16 patients with hemophilia A with inhibitor (HAwI) and 10 patients with hemophilia B with inhibitor (HBwI). A total of 9 patients with HAwI and 8 patients with HBwI were randomized to concizumab PPX.
  - Patients received a concizumab loading dose of 0.5 mg/kg followed by 0.15 mg/kg daily. Patients treated with concizumab who did not bleed one week after starting concizumab received a single 90 µg/kg dose of eptacog alfa (rFVIIa).
  - Dose escalations to 0.20 and 0.25 were allowed in patients who did not respond.
    - Two patients (One with HAwI and one in HBwI) received dose escalation to 0.20 mg/kg.
    - One patient discontinued from the rFVIIa on-demand arm after 70 days of treatment in the main phase.
  - All other on-demand patients have transferred to the extension phase where they are receiving concizumab PPX.

The primary endpoint will be the number of bleeds over 24 weeks' time. The comparison of the number of bleeds over time between the group randomized to receive concizumab prophylaxis versus no prophylaxis will be performed using a negative binomial regression model. The primary endpoint was analyzed for HAwI and HBwI together, i.e. all patients in the trial.

The key secondary endpoints were:

- Number of spontaneous bleeding
- Number of TEAEs.

Schematic of Trial NN7415-4310 conducted in HAwI and HBwI patients



b. Include any additional relevant information. Consider the following in your response:

- Explain whether the data provided should be considered preliminary clinical evidence of a substantial improvement over available therapies. In all cases, actual results, in addition to reported significance levels, should be shown. Describe any identified deficiencies in the trial that decrease its persuasiveness.
- Identify any other factors regarding the clinical development program that were taken into consideration when evaluating the preliminary clinical evidence, such as trial conduct, troublesome and advantageous aspects of the design, missing data, any relevant nonclinical data, etc.
- Safety data: Provide a brief explanation of the drug's safety profile, elaborating if it affects the Division's recommendation.

The efficacy data provided shows preliminary evidence of a significant improvement for prophylaxis in patients with hemophilia B with FIX inhibitors over on demand treatment (rFVIIa) and may demonstrate substantial improvement over existing therapy. Comparison to approved therapy for the same indication (FEIBA) can not be made due to the limited data available on the efficacy of FEIBA in patients with hemophilia B with inhibitor. Only one patient out of 3 patients with hemophilia B with inhibitor exposed to FIEBA in the pivotal trial which was used to support FEIBA approval. FEIBA have limited utility in practice in patients with HBwI because FEIBA exposure, contains FIX, increase the inhibitor titer and may induce hypersensitivity and anaphylactic reaction (anamnestic response).

The analysis of the effect of concizumab on the annualized bleeding rate (ABR) during the main phase of 24 weeks of treatment has been completed. There was a 51% and 61% reduction in the mean and median ABR in patients with HBwI, respectively. However, the mean and median rates of ABR reduction were higher when compared ABR rates of patients with HBwI to all control patients (HAWI and HBwI) who received on demand treatment with rFVIIa (70%, 74%, respectively).

Annualized bleeding rates during main phase - bleeds occurring by last dose level – full analysis set

| Hemophilia Type           |                |                  |                  |
|---------------------------|----------------|------------------|------------------|
| Type of treatment receive | HBwI           |                  | HAWI and HBwI    |
|                           | Concizumab PPX | rFVIIa on demand | rFVIIa on demand |

| Number of patients       | N = 8          | N = 2            | N = 9            |
|--------------------------|----------------|------------------|------------------|
| ABR, Mean (SD)           | 6.3 (3.8)      | 13.0 (6.2)       | 21.1             |
| Median (Min; Max)        | 5.1 (3.4; 6.9) | 13.0 (8.6; 17.4) | 19.7 (6.6; 36.5) |
| The Mean ABR reduction   | 51%            |                  | 70%              |
| The Median ABR reduction | 61%            |                  | 74%              |

Supportive evidence:

- Trial 4310 results showed that the median ABR in patients with HAwI and HBwI who received concizumab was 4.5 compared to 19.7 those who received on demand treatment with rFVIIa. This represent a 78% reduction in bleeding.
- The median ABR in patients with 17 patients with HBwI and HAwI (9 patients with HAwI and 8 with HBwI) who received concizumab for routine prophylaxis was compared to that of 19 patients with HAwI and HBwI (18 patients with HAwI and 1 with HBwI) who received FEIBA for routine prophylaxis (study was used to support the prophylaxis indication of FEIBA). The median ABR of concizumab was 4.5 compared to a median ABR of 7.9 for FEIBA which represent a reduction of 45%.
- The subcutaneous route of administration is an improvement in burden of treatment for these patients compared to the other approved prophylaxis therapy (FEIBA) which should be administered IV.
- Importantly, concizumab has no structural relationship to FVIII and no potential to induce or enhance the development of direct inhibitors to FVIII may have an advantage in reducing the occurrences of hypersensitivity and anaphylactic reaction reported with FEIBA.

**12. Division's recommendation and rationale (pre-MPC review):**

☒ GRANT :

Provide brief summary of rationale for granting:

Hemophilia B with inhibitor is a serious and life threatening disease with unmet medical need. Concizumab therapy has no structural relationship to FIX, unlike the approved FEIBA for this indication which contains FIX and known to increase the FIX inhibitor titers and increased the risk of hypersensitivity and anaphylactic reaction.

Preliminary clinical evidence suggested that concizumab for prophylaxis is effective in patients with HBwI in reducing bleeding episode in comparison to on demand treatment in patients with HBwI or combined HAwIa and HBwI. Concizumab prophylaxis resulted in 61% and 74% reduction in the median annualized bleeding rate (ABR) in patients with HBwI compared to the ondemand control group (patients with HBwI or combined HAwI and HBwI), respectively. The clinical evidence suggested that concizumab prophylaxis lead to reduction in bleeding rate in patients with hemophilia A and hemophilia B with inhibitors.

In addition, in inpatients comparison of concizumab prophylaxis to historical before and after treatment in patients with HBwI showed a 80% reduction in median annualized bleeding rate (ABR). The subcutaneous route of administration is an improvement in burden of treatment for these patients compared to the other approved prophylaxis therapy (FEIBA) which should be administered IV.

*Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.*

☐ DENY:

Provide brief summary of rationale for denial:

Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:

**13. Division's next steps and sponsor's plan for future development:**

- a. *If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):*

The design of the registrational phase 3 trial will be discussed during the upcoming Meeting with the sponsor in March 2019.

- b. *If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:*

**14. List references, if any:**

1. Di Michele, D. (2007). Inhibitor development in haemophilia B: an orphan disease in need of attention. *British Journal of Haematology*, 305-315.
2. Katz, J. (1996) Prevalence of FIX Inhibitors among patients with hemophilia B: results of large scale North America survey. *Haemophilia*, 2, 28–31.
3. Ljung, R., Petrini, P., Tengborn, I. & Sjorin, E. (2001) Haemophilia B mutations in Sweden: a population based study of mutational heterogeneity. *British Journal of Haematology*, 113, 81–86.
4. Antunes SV, Tangada S, Stasyshyn O, Mamonov V, Phillips J, Guzman-Becerra N, et al. Randomized comparison of prophylaxis and on-demand regimens with FEIBA NF in the treatment of haemophilia A and B with inhibitors. *Haemophilia*. 2014;20(1):65–72.

**15. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting?** YES ☐ NO ☐

**16. Clearance and Sign-Off (after MPC review):**

Grant Breakthrough Therapy Designation ☐  
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}  
Team Leader Signature: {See appended electronic signature page}  
Division Director Signature: {See appended electronic signature page}

**Revised 10/3/18/M. Raggio**

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
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/s/  
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SALEH AYACHE  
03/06/2019 04:37:41 PM

KATHY M ROBIE SUH  
03/06/2019 05:49:40 PM

ANN T FARRELL  
03/06/2019 05:52:40 PM